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In Translation

Stem Cells and Osteoporosis Therapy

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Skeletal remodeling requires recruitment of osteoblast precursors, in the form of MSCs, to the bone surface. In this issue of *Cell Stem Cell*, Wu et al. (2010) demonstrate that this event is mediated by osteoclastic mobilization of active transforming growth factor β1, which is inhibited by a common antiosteoporosis drug.

Osteoporosis is endemic in developed countries; approximately half of 65-year-old white or Asian women ultimately experience a spontaneous fracture. Regardless of cause, osteoporosis results from an imbalance of osteoclasts and osteoblasts, wherein the net activities of the former supersede the latter. Thus, osteoporosis therapy involves either suppression of bone resorption or stimulation of formation. The discovery that intermittent administration of parathyroid hormone (PTH) stimulates bone formation yielded the first and only bone anabolic drug (Neer et al., 2001), but the most common approach to preventing and treating osteoporosis is osteoclast inhibition.

Osteoclasts and osteoblasts have an interdependent relationship; the recruitment of each depends upon the other. Osteoclasts differentiate from macrophage precursors under the aegis of RANK ligand and M-CSF, produced by osteoblast lineage cells. On the other side of the equation, it is the bone-resorbing activity of osteoclasts that attracts osteoblasts to the bone surface, a process known as skeletal remodeling. This ever-occurring event consists of focal removal and subsequent replacement of bone. Thus, bone remodeling is characterized by tethering of osteoclast and osteoblast recruitment and function. If remodeling is imbalanced and the magnitude of resorption surpasses formation, osteoporosis ensues.

Patients lose bone by two general mechanisms that are dictated by remodeling kinetics. Estrogen deficiency, which represents the most common cause of osteoporosis, is a high turnover state in which both formation and resorption are accelerated, but the relative activity of the osteoclast is greater than that of the osteoblast. Consequently, suppression of the osteoclast by hormone replacement had been the standard of care for decades. With the realization that estrogens increase risk of breast cancer and cardiovascular complications in older women, bisphosphonates, which directly target osteoclasts, have become the most common treatment for postmenopausal osteoporosis. Given the absolute increase in osteoclast activity in estrogen-deficient osteoporosis, the effectiveness of bisphosphonates is not surprising. These drugs are nonhydrolyzable pyrophosphate analogs that bind bone mineral with extremely high affinity and reside within the skeleton until mobilized by osteoclasts. Alendronate, the most commonly administered bisphosphonate, maintains bone mass and reduces fracture risk of postmenopausal, osteoporotic women for as long as a decade with minimal complications in the great majority of patients (Bone et al., 2004). The capacity of bisphosphonates to enhance bone mass reflects the fact that it incapacitates osteoclasts and thus dampens remodeling.

The most common secondary form of osteoporosis is that induced by glucocorticoids, but its skeletal dynamics are distinctly different than those resulting from estrogen deprivation. Whereas bone remodeling is accelerated with menopause, it is suppressed by prolonged administration of glucocorticoids. Thus, glucocorticoid-induced osteoporosis represents a low remodeling form of the disease in which both formation and resorption are suppressed but the former is more so than the latter. Stimulation of bone formation by intermittent PTH administration represents the most effective current approach to this condition, but most patients are treated with bisphosphonates, which further suppress remodeling.

Because osteogenesis is coupled to resorption in the remodeling process, alendronate's antiosteoclastic properties blunt the bone-forming capacity of simultaneously administered PTH (Black et al., 2003). Because the principal role of remodeling is probably to replace effete bone with new, its prolonged suppression probably compromises the skeleton's biomechanical properties and evidence indicates such is the case with alendronate (Allen and Burr, 2007). Thus, understanding the specific mechanism by which bisphosphonates suppress osteoclast activity is central to developing antiresorptive strategies that spare bone formation.

Although remodeling has been known for decades to be essential for skeletal integrity, the means by which osteoclasts recruit osteoblasts to the site of resorption is among the most important yet enigmatic issues regarding skeletal biology and treating osteoporosis. Last year Tang et al. (2009) demonstrated that active TGF-β1 is a likely molecule attracting osteoblasts to sites of prior osteoclast activity. In this scenario, the activated growth factor, mobilized from bone matrix by osteoclasts, establishes a gradient that attracts $Sca1^{+}CD29^{+}CD45^{-}CD11b^{-}$ mesenchymal stem cells to sites of bone resorption where they putatively undergo osteoblast differentiation. In the current issue of *Cell Stem Cell*, the same group extends these observations to the practical issue of treating osteoporosis with bisphosphonates (Wu et al., 2010).

To determine the mechanism by which alendronate blunts bone formation, Wu et al. (2010) first asked whether the drug arrests PTH-stimulated osteoblast differentiation. This model was not supported by their results, despite observing reduced osteogenesis and a decreased number of bone-forming cells, in vivo, a circumstance reminiscent of absence

of active TGF-β1, which recruits osteoblast precursors to the bone surface (Tang et al., 2009). In fact, the authors found that although the abundance of total TGF-β1 in bone marrow is unaffected by treatment with PTH and alendronate, alone or in combination, the hormone increases the active state of the growth factor while the bisphosphonate reduces it. This outcome is mirrored by the number of cells expressing Smad2/3, which this group established mediates migration of osteogenic precursors to remodeling sites (Tang et al., 2009). The authors also find that absence of TGF-β1, in mice, prevents PTH-stimulated bone formation. Alendronate does not alter differentiation of TGF-$\beta1^{-/-}$ osteoblasts, in vitro, but reduces their PTH-stimulated abundance, in vivo. Thus, the bisphosphonate, whose sole established direct target in vivo is osteoclasts, probably inhibits bone formation by arresting active TGF-β1 mobilization from bone matrix, thereby preventing recruitment of mesenchymal stem cells to remodeling sites. Expanding upon their previous observations, the authors propose that the target osteoblast precursors cells are $Sca1^+CD29^+CD45^-CD11b^-$. To determine whether such is the case, they isolated and expanded multipotential mesenchymal cells with this phenotype. Confirming their osteogenic capacity, in vivo, these cells form bone when placed under the renal capsule. Finally, the authors demonstrate that TGF-$\beta1^{-/-}$ mice fail to normally recruit $Sca1^+CD29^+CD45^-CD11b^-$ cells to the bone surface in response to PTH. These studies indicate that alendronate suppresses PTH-stimulated bone formation by inhibiting osteoclast-mediated mobilization of active TGF-β1, thereby reducing migration of osteoblast precursors to sites of remodeling (Figure 1).

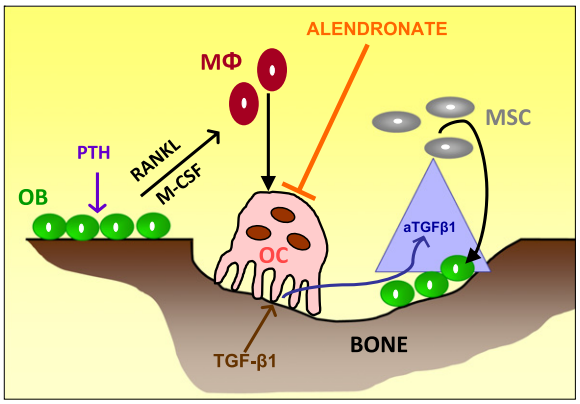

Figure 1. Alendronate Suppresses PTH-Stimulated Bone Formation by Inhibiting Osteoclast-Mediated Mobilization of Activated TGF-β1

PTH stimulates osteoblasts (OB) to produce RANKL and M-CSF. These cytokines induce marrow macrophage lineage cells (MΦ) to differentiate into mature osteoclasts (OC) that initiate remodeling by resorbing a focal packet of bone. Latent TGF-β1 is mobilized from resorbed bone and activated by the osteoclast. A gradient of activated TGF-β1 (aTGF-β1) recruits osteoblast precursors in the form of $Sca1^+CD29^+CD45^-CD11b^-$ mesenchymal stem cells (MSC) to the remodeling site where they differentiate into osteoblasts that replace the previously resorbed bone. Alendronate directly inhibits osteoclasts, thereby arresting TGF-β1 mobilization and thus bone formation.

Currently, osteoporosis patients are limited to 2 year cycles of PTH treatment. Thus, a logical strategy to prevent loss of accumulated bone is to utilize an antiresorptive agent between episodes of PTH administration (Black et al., 2005). Wu et al. (2010) predict that unlike simultaneous administration of the two drugs, this sequential strategy will not suppress bone formation because osteoclast-mediated mobilization of TGF-β1 will be intact during PTH-only cycles (Tang et al., 2009). This hypothesis is challenged, however, by the decade-long persistence of bisphosphonates in the skeleton after cessation of their administration (Drake et al., 2008). The elegant experiments of the Cao laboratory underscore the necessity of developing short-acting antiresorptive agents that will permit recovery of osteoclast-mediated mobilization of the growth factor during the period of anabolic therapy (Wu et al., 2010, this issue; Tang et al., 2009). The translation of observations in mice into current antiosteoporosis drugs holds promise that the present studies will yield the same (Eisman et al., 2010; McClung et al., 2006).

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